ESTIMATION OF RISK IN THE FIELD OF OSTEOPOROSIS

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ABSTRACT

Introduction: Osteoporosis has been recognised as an established and well-defined disease that affects more than 75 million people in the United States, Europe and Japan. Osteoporosis has been operationally defined by the WHO on the basis of bone mineral density (BMD) assessment. Although risk factors for fracture are well-known and thoroughly investigated, osteoporosis is an under-diagnosed and under-treated disease in women, and even more so in men.

Objective: The general objective of this work is in the context of the development an assessment tool (FRAX) for the prediction of fracture in men and women with the use of clinical risk factors for fracture with and without the use of femoral neck BMD. The rationale arises from the observation that factors other than BMD contribute towards fracture risk and that estimates of probability permit the integration of multiple clinical risk factors (CRFs) including the competing risk of death. The material presented in this thesis aims to illustrate several components of this work. The first is the identification of a clinical risk factor (exposure to glucocorticoids) as a potential candidate for its inclusion into the FRAX algorithm. A second aim was to determine the increase in operating characteristics of combining clinical risk factors with and without the inclusion of BMD. A novel feature of the FRAX models is that they integrate the fracture and death hazards in the determination of fracture probabilities. Several clinical risk factors affect the death hazard as well as the fracture hazard, so that a third aim was to explore the effect of a well established CRF (BMD) and a potential CRF (serum 25-hydroxyvitamin D) on the risk of death. A final aim was to determine the potential of a new candidate risk variable (serum adiponectin) for fracture.

Methods: To create the risk assessment tool baseline and follow-up data is used from eleven international prospective population-based cohorts comprising 15 259 men and 44 902 women with 5 563 fractures of any kind and 978 hip fractures. Cohorts were followed for a total of over 250 000 person years. Primary data from the cohorts is used so that important interactions could be determined. In addition a Swedish cohort of 3 014 elderly men (MrOS) is used, drawn from the general population.

Results: The risk factors incorporated in the assessment tool comprised body mass index (as a continuous variable), a prior history of fracture, a parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis, current smoking and alcohol intake >2 units daily. Their inclusion was based on their international validity and independent contribution to fracture risk. Four models were then constructed to compute fracture probabilities in nine of the cohorts. These comprised the probability of hip fracture, with and without femoral neck BMD, and the probability of other osteoporotic fractures, with and without BMD. For each model fracture and death hazards functions were computed and used to compute 10-year fracture probabilities (FRAX). The model could be calibrated to any country where the epidemiology of fracture and death is known. In the publications included in this thesis, exposure to glucocorticoids is shown to be a significant risk factor for fracture, providing the rational for the inclusion of this CRF in the FRAX algorithms. We also show that the incorporation of CRFs improves the operating characteristics of fracture risk assessment over and above that provided by BMD alone. In elderly men in the Swedish MrOS cohort, it is shown that low BMD is associated with increased mortality in a non-linear pattern (overall gradient of risk (GR) 1.27; 95% CI 1.14-1.42, multivariable adjusted), that low vitamin D is associated with increased mortality (overall GR; 1.15; 95% CI 1.03-1.29, multivariable adjusted) and that the association wanes with time. It is also shown that high adiponectin is associated with higher fracture risk in elderly men (overall GR; 1.32; 95% CI 1.15-1.52, multivariable adjusted).

Conclusion: Components of the work in this thesis have contributed to the creation of FRAX, a fracture risk assessment tool, that has been recommended by WHO and is widely used in clinical practice to identify patients suitable for pharmacological intervention. In elderly men it is showed that low BMD and low vitamin D are risk factors for death and high adiponectin is a risk factor for fracture. The biostatistical contribution to these associations is the identification of non-linearity of the associations and their dependence on time since baseline assessment.

Keywords: osteoporosis, fracture, bone mineral density, clinical risk factors, FRAX, Poisson model, 10 year probability, mortality, vitamin D, adiponectin

List of papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I **A Meta-Analysis of Prior Glucocorticoid Use and Fracture Risk.**
Kanis JA, Johansson H, Odén A, Johnell O, De Laet C, Melton LJ, Tenenhouse A, Reeve J, Silman AJ, Pols H, Eisman JA, McCloskey EV, Mellström D.
J Bone Miner Res 2004; 19 (6): 893-99.

II **The use of clinical risk factors enhance the performance of BMD in the prediction of hip and osteoporotic fractures in men and women.**
Kanis JA, Odén A, Johnell O, Johansson H, De Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S, Eisman JA, Fujiwara S, Glüer C, Goltzman D, Hand D, Krieg MA, La Croix A, McCloskey EV, Mellström D, Melton LJ, Pols H, Reeve J, Sanders K, Schott AM, Silman A, Torgerson D, van Staa K, Watts NB, Yoshimura N.
Osteoporosis International. 2007; 18(8): 1033-1046.

III **Low bone mineral density is associated with increased mortality in elderly men: MrOS Sweden.**
Johansson H, Odén A, Kanis J, McCloskey EV, Lorentzon M, Ljunggren Ö, Karlsson MK, Orwoll E, Tivesten Å, Ohlsson C, Mellström D
Osteoporosis International 2010

IV **Low serum vitamin D is associated with increased mortality in elderly men. MrOS Sweden**
Johansson H, Odén A, Kanis J, McCloskey E, Lorentzon M, Ljunggren Ö, Karlsson MK, Tivesten Å, Barrett-Connor E, Ohlsson C, Mellström D
Submitted

V **High serum adiponectin predicts incident fractures in elderly men. Mr OS Sweden.**

Johansson H, Odén A, Lerner U, Jutberger H, Lorentzon M, Barrett-Connor E, Karlsson M, Ljunggren Ö, Smith U, McCloskey E, Kanis J, Ohlsson C, Mellström D

Not submitted

Table of contents

Abbreviations and explanations

25(OH)D	25-hydroxy-vitamin D
CRF	clinical risk factor
BMD	bone mineral density
BMI	body mass index (kg/m$^{2)}$. Calculated: weight in kg / height in m^2
BUA	broad-band ultrasound attenuation
CI	confidence interval
DXA	dual-energy X-ray absorptiometry
FRAX	WHO fracture assessment tool
GR	gradient of risk, hazard ratio per one SD change
HR	hazard ratio
ICD 10	International Classification of Diseases, Revision 10 (1990)
MrOS	study of osteoporotic fractures in men
QUS	quantitative ultrasound
SD	standard deviation
SoS	speed of sound (or ultrasound velocity)
T-score	Bone density values in individuals expressed in relation to the young healthy population in standard deviation units.
WHO	World Health Organization

Introduction

Risk

In epidemiology, a risk factor is a variable associated with an increased risk of disease. Risk factors are correlational and not necessarily causal, because correlation does not imply causation. Risk factors are evaluated by comparing the risk of those exposed to the potential risk factors to those not exposed. The term ñrisk factorò was first coined by heart researcher Thomas Dawber in a scientific paper in 1961, where he attributed heart disease to specific conditions (blood pressure, cholesterol and smoking). More generally, a risk variable can be considered, which is allowed to be discrete or continuous, and study the relationship for the risk of an event.

Survival analysis examines the time it takes for events to occur. The prototypical event is death, from which the name ñsurvival analysisò and much of its terminology derives, but the application of survival analysis is much broader. Survival analysis focuses on the distribution of survival times. A basic notion of survival analysis is hazard function, which describes the momentary risk of an event. Survival time assumes a starting point from which the survival is counted. By use of hazard functions risk can be studied without survival times and thus the applicability can be extended. Cox proportional-hazards regression model (introduced in a seminal paper by Cox, 1972)[1], is a broadly applicable and the most widely used method of survival analysis. The proportional hazard requirement of the Cox model means that the hazard ratio when comparing a value of a risk variable with another value is not dependent on time. This may sometimes be a serious limitation when it is relevant to study the predictive ability of a risk variable with time or when a treatment effect changes with duration of treatment. From a mathematical point of view, the proportional hazards requirement can be described as follows: The ß-coefficients must not depend on time. For the studies in the present thesis, a method is applied which overcome the restriction of proportional hazards referred to the method as a Poisson regression analysis[2]. Some comments are needed to explain how Poisson regression was presented in Breslow and Day[2] and how it has been used to estimate a continuous hazard function. In Breslow and Day the intention was to estimate the expected number of events, e.g. the number of diseased, depending on variables that characterize subpopulations. Our aim has been to estimate hazard functions.

The follow-up period of each individual is divided in to small intervals. The number of events of an individual in an interval is 0 or 1, the last mentioned value is attained with a low probability. The distribution of such a variable coincides almost exactly with a Poisson distribution. That will not always be the case if the intervals are wide or the number of events include several individuals. In Breslow and Day[2] they did not confine the model building to one individual at a time and small intervals ensure Poisson distribution.

Studies of risk in the medical field are often a collaboration between experts in medicine and statistics. On rare occasions statisticians can contribute with novel methods, which elucidate new aspects of risk variables and allows the complex use of them. In this thesis, some novel methods have been applied to determine whether a relative change in risk is the same for an increase of 1 unit from the value x of the risk variable independently of x. The same principles can be used to study if there is an interaction between a risk variable and time. Whereas the traditional methods generate a simple hazard ratio only, these new methods can produce functions of time or of the risk variable or both. Finally the methods permit estimation of continuous hazard functions, which can be used in several applications.

Osteoporosis

Osteoporosis has been recognised as an established and well-defined disease that affects more than 75 million people in the United States, Europe and Japan. Osteoporosis causes more than 8.9 million fractures annually world-wide of which more than 4.5 million occur in the Americas and Europe. The life-time risk for a forearm, hip or vertebral fracture has been estimated to be in the order of 30 to 40% in the Western World ï in other words, very close to that for cardiovascular disease. Osteoporosis is not only a major cause of fractures, it also ranks high among diseases that cause people to become bedridden with serious complications. These may be life threatening in the elderly. Because of the morbid consequences of osteoporosis, the prevention of this disease and its associated fractures is considered essential to the maintenance of health, quality of life, and independence in the elderly population.

Osteoporosis has been operationally defined on the basis of bone mineral density (BMD) assessment. A WHO study group that was chaired by Prof John Kanis defined osteoporosis in 1994 for postmenopausal women as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of <-2.5 SD)[3 4]. This criterion has been

widely accepted and, in many countries, provides both a diagnostic and intervention threshold. Suitable diagnostic cut-off values for osteoporosis in men have been less well defined. Many investigators and equipment manufacturers have reported T-score values that use a male reference range, which in turn has led to a T-score of -2.5SD being used widely as a diagnostic criterion also for men. The most widely validated technique to measure BMD is dual energy X-ray absorptiometry (DXA) in hip and lumbar spine, and diagnostic criteria, based on the T-score for BMD are a recommended entry criterion for the development of pharmaceutical interventions in osteoporosis. The implication is that BMD should be assessed before treatment is considered.

There are, however, problems with the use of BMD tests alone. In many countries, BMD tests using DXA are not widely available, or are used predominantly for research, in part because of the high capital costs of DXA. Another problem with the use of BMD tests alone is that they can only capture one aspect of the risk of fracture in a disease that is multifactorial. In the case of osteoporosis, assessment with BMD captures a minority of the fracture risk. For example the annual incidence of hip fracture increases approximately 30-fold between the ages of 50 and 90 years, but from the known relationship between BMD and fracture risk and the loss of bone with age, it is expected that hip fracture risk would rise only 4-fold[5-7]. Thus, the increase in risk with age is approximately 7-times greater than can be explained on the basis of bone mineral density alone.

The imperfect capture of risk with BMD alone poses several problems. In the context of population screening with BMD alone, the performance characteristics of the test are inadequate in terms of the trade-off between sensitivity and specificity [4 8]. Osteoporotic fractures affect a substantial minority of the population, and intervention thresholds based on BMD alone lack sensitivity over most reasonable assumption ï i.e. the detection rate is low. The use of other risk factors for fracture in addition to BMD improves sensitivity without adverse effects on specificity [8]. Against this background there has been interest in computing risk of clinical outcomes based on combinations of risk factors [8 9]. Indeed, it is suggested that intervention thresholds in osteoporosis should be based on fracture probabilities rather than the fulfilment of diagnostic criteria using BMD alone [10]. This approach also enfranchises all risk factors of proven clinical utility, as has been done for cardiovascular disease [11 12].

Estimation of risk

Conroy et al determined the 10-year probability of fatal cardiovascular disease as a function of age, blood pressure and cholesterol (SCORE)[13]. The UKPDS group[14] has determined the probability of coronary heart disease among patients with Type II diabetes depending on a set of variables. The same group has also determined the probability of stroke as a function of age, race, smoking, body mass index, atrial fibrillation, HbA1c, systolic blood pressure, ratio of total to HDL cholesterol and duration of diabetes. In these examples, the risk of dying from other reasons was not taken into account. Thus they have for example calculated the risk of stroke (fatal or non fatal), which does not allow for the fact that the patients might die for other reasons. This limitation is inappropriate in the case of hip fracture for instance, since hip fracture is common among people at very high age. The same would hold true for elderly patients with diabetes. In such cases it would also be appropriate to calculate the probability of stroke taking the risk of dying into account. In the context of osteoporosis, there are two tools other than FRAX for fracture risk calculation, QFractureÊ (www.qfracture.org) based on a UK cohort[15] and the Garvan tool (www.garvan.org.au) based on a cohort from Australia[16 17]. Both uses Cox proportional hazard regression models and neither take account of the competing risk of death.

A further problem in the construction of risk assessment models relates to the use of hazard functions determined for one geography to other countries where the hazards of death and disease events differ. The incidence of hip fracture varies 15-fold around the world[18] and to be able to use the fracture probability estimated from an international setting to a specific country, a modification of the probability has to be done according to the country-specific epidemiology.

In the past decade, a great deal of research has taken place to identify factors other than BMD that contribute to fracture risk. Examples include age, sex, the degree of bone turnover, a prior fracture, a family history of fracture and lifestyle risk factors such as physical inactivity and smoking. Some of these risk factors are partially or wholly independent of BMD. Independent risk factors used with BMD could, therefore, enhance the information provided by BMD alone. Conversely, some strong BMD-dependent risk factors can, in principle, be used for fracture risk assessment in the absence of BMD tests. For this reason, the consideration of

well-validated risk factors, with or without BMD, is likely to improve fracture prognostication and the selection of individuals at high risk for treatment.

In this thesis the work on constructing WHO fracture assessment tool (FRAX) is described. FRAX is based on 11 prospectively studied population-based cohorts. In those cohorts there was 25% men (n=15 259). The Osteoporotic Fractures in Men (MrOS) Study is a prospective cohort study designed to provide information about osteoporosis and fracture risk in men. The MrOS cohort is studied in this thesis to elucidate risk factors for fracture and death in men.

Vitamin D

Vitamin D is recognized to be an active hormone with endocrine and paracrine effects on many organs and tissues of the body. The two natural sources of vitamin D are sunlight and nutrition[19 20]. Vitamin D_3 (cholecalciferol) is the form of vitamin D that is synthesized in the skin under the influence of ultraviolet B (UVB) rays; it is also found in certain fish, fortified dairy products, and most dietary supplements. Vitamin D_2 (ergocalciferol) is produced by irradiated fungi and is the form of vitamin D found in some prescription supplements. After vitamin D is formed in the skin, it is converted to 25(OH)D (calcidiol) in the liver. This transport and storage form of vitamin D then circulates to the kidneys, where it is converted to the active form (1Ŭ,25$[OH]_2$D); calcitriol). Calcitriol is the active form of vitamin D, which binds to vitamin D receptors in intestines, bones, and kidneys to increase calcium absorption from the intestines, promote calcium deposition in bones and decrease parathyroid hormone concentration (PTH). The transport and storage form of vitamin D, 25(OH)D, is measured to assess the vitamin D sufficiency status of persons. Several studies have described a relationship between 25(OH)D and the risk of death[21-35].

Adiponectin

Adiponectin is a protein hormone mainly produced by adipocytes (fat cells) that regulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin influences the bodyŏs response to insulin. Adiponectin is secreted into the bloodstream where it accounts for approximately 0.01% of all plasma protein. In cross sectional studies, higher serum adiponectin has generally been associated with lower BMD values in women[36-46]. There are five studies about adiponectin and fracture risk, two cross-sectional studies[47 48] and three prospective studies[42 49 50]. The studies that included women

found no significant association between adiponectin and risk of fracture [42 47 48 50]. Three studies found a positive significant association between adiponectin and risk of fracture among men[42 48 50] whilst one study found no significant interaction[49].

Aim

The general aims of this thesis were to identify and validate clinical risk factors for use in fracture risk assessment on an international basis, either alone, or in combination with bone mineral tests. Both risk factors for fracture and death are identified. A further aim was to develop algorithms for risk assessment (FRAX) that were sufficiently flexible to be used in the context of many primary care settings, including those where BMD testing was not readily available. Further general aim was to investigate other risk variables for fracture and death in a setting of elderly men.

The specific aims were:

I. To examine, in an international setting, the association between glucocorticoid use and fracture risk, in men and women and to determine its dependence on other risk factors.

II. Utilise the primary data from the eleven international cohorts to determine the impact of the addition of multiple clinical risk factors to BMD for the prediction of fractures, and to validate the findings using data from independent cohorts.

III. To investigate the relationship between BMD and mortality in elderly men in MrOS cohort, Sweden.

IV. To investigate the relationship between vitamin D and mortality in elderly men in MrOS cohort, Sweden.

V. To investigate the relationship between adiponectin and risk of fracture in elderly men MrOS cohort, Sweden.

Patients and methods

60 161 persons are studied, 15 259 men and 44 902 women from 11 prospectively studied cohorts with 5 563 fractures of any kind and 978 hip fractures. Cohorts were followed for a total of over 250 000 person years. Brief details of the cohorts studied are given below more extensively descriptions are given in paper I and II.

OFELY

The OFELY cohort comprises an age-stratified cohort of 1 039 women aged 31-89 years randomly selected from the regional section of a large health insurance company (Mutualle Generale dõEducation Nationale, Lyon) [51]. Eighteen percent of women contacted participated in the study.

EVOS

The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centres in 19 European countries [52-54]. Equal numbers of men and women were drawn in each centre within six 5-year age bands (50-54 to 75-79 years).

CaMos

The Canadian Multicentre Osteoporosis Study (CaMos) is an on-going prospective age-stratified cohort. The study is documenting the incidence of fractures and risk factors in a random sample of 9 424 men and women aged 25 years or more selected by telephone listings. The sampling frame is from 9 study centres in 9 provinces [55].

Rochester

The Rochester cohort was recruited from two random US population samples stratified by decade of age, one comprising women who were subsequently followed for up to 20 years [56] and another sample of women and men followed for 8 years [57].

Sheffield

The Sheffield cohort comprised women aged 75 years or more selected randomly from the population of Sheffield, UK, and surrounding districts between 1993 and 1999. The women

were randomly allocated to treatment with the bisphosphonate clodronate, or to an identical placebo. The present paper comprised 2148 women allocated to treatment with placebo [58].

Rotterdam

The Rotterdam study, begun in 1990, is a prospective cohort study that aimed to examine and follow-up all residents aged 55 years and older living in Ommoord, a district of Rotterdam [59] [60]. For this analysis, validated fracture follow up was available for 7774 participants (3065 men) with an average follow up time of 6 years.

Kuopio

The Kuopio osteoporosis risk factor and prevention (OSTPRE) study in Finland comprised a postal enquiry sent to all 14,220 women aged 47-56 who were residents of Kuopio province in 1989. 13,100 women responded to the enquiry, of whom 1214 were excluded for incomplete information. This left a study population of 11,886 women[61].

Gothenburg I

This study comprised 4 birth cohorts of 2375 randomly sampled men and women aged 70 years or more followed for up to 20 years at Gothenburg [62] [63] after a base-line BMD measurement. The participants were drawn randomly from the population register in Gothenburg by the date of birth to provide cohorts aged 70, 76, 79 and 85 years at the time of investigation.

Gothenburg II

The Gothenburg study comprised a randomly drawn population cohort of women aged 21-89 years followed up to 7.9 years (mean 4.2 years)[64]. 70% of those invited (approximately 7000 women) participated in the study that examined risk factors for osteoporosis.

DOES

The DOES Osteoporosis Epidemiology Study (DOES) is a population-based study with multiple assessments of skeletal status in men and women aged 60 years or more from DOES, Australia [65]. Participation in the study was 56% of the population.

Hiroshima

The Adult Health Study in Hiroshima (AHS) documents the late health effects of radiation exposure among atomic bomb survivors in Hiroshima and Nagasaki. AHS subjects have been followed through biennial medical examinations since 1958 with a participation rate of approximately 80% throughout this period [66 67].

In paper I just EVOS, CaMos, Rotterdam, DOES, Sheffield, Rochester and Gothenburg II is used since the baseline assessment in these cohorts included questions about the use of glucocorticoids.

In paper II all cohorts except Ofely and Kuopio were used. These two cohorts were excluded since they didnôt have enough clinical risk factors available in their baseline assessment. For evaluation of the risk score additional independent cohorts were used; EPIDOS, PERF, THIN, OPUS, York, SOF, Geelong I, Geelong II, Miyama, SEMOF and WHI described in more detail in paper II.

In paper III and IV MrOS Sweden is used, a multi-centre study including elderly men aged 70-80 years. The cohort was conducted with the aim of getting more information on osteoporosis and risk factors for osteoporosis in men. In paper V just the part from Gothenburg in MrOS is used. Participants in MrOS Sweden were randomly identified using national population registers. To be eligible for the study, men had to be able to walk without aids, provide self-reported data and give signed informed consent. The participation rate was 45%. MrOS Sweden is part of a multicentre study including men in Sweden (n=3014), Hong Kong (n=2000) and the United States (n=6000). More details are given in paper III-V.

Baseline and outcome variables

In the cohorts a questionnaire was answered at baseline. This questionnaire were not standardized between cohorts and the clinical risk factors analysed could be present or not and the questions could be differently asked.

Paper I focused on ever oral glucocorticoid use, because the questionnaire in most cohorts did not distinguish between ever and current use.

EVOS ï ever use for more than 3 months

CaMos ï ever use of more than 1 month

Rotterdam ï current use and noncurrent use
DOES ï never use, past use and current use
Sheffield ï never use, ever use and current use
Rochester - ever use of more than 6 months
Gothenburg II ï ever use of more than 3 months

BMD was assessed at the femoral neck by DXA with the exception of the two cohorts from Gothenburg where BMD was assessed by DXA at the distal forearm.

The fracture outcome during follow up were divided into three categories; any fracture, hip fracture and osteoporotic fracture. These categories could look somewhat different for different cohorts but any fracture was all fractures reported and an osteoporotic fracture that was one considered to be characteristic for osteoporosis[68]. When a country specific model is made for the ten year risk of fracture, the ten year risk of a major osteoporotic fracture and the ten year risk of a hip fracture is calculated. A major osteoporotic fracture is a clinical spine, hip, humeral or forearm fracture. A clinical spine fracture is defined as ICD 10 codes S12.0 (Fracture of first cervical vertebra), S12.1 (Fracture of second cervical vertebra), S12.2 (Fracture of other specified cervical vertebra), S22.0 (Fracture of thoracic vertebra), S22.1 (Multiple fractures of thoracic spine), S32.0 (Fracture of lumbar vertebra) and T08 (Fracture of spine, level unspecified). A humeral fracture is defined as ICD 10 codes S42.2 (Fracture of upper end of humerus) and S42.3 (Fracture of shaft of humerus). A forearm fracture is ICD 10 codes S52.5 (Fracture of lower end of radius) and S52.6 (Fracture of lower end of both ulna and radius). A hip fracture comprised ICD 10 codes S72.0 (Fracture of neck of femur), S72.1 (Pertrochanteric fracture) and S72.2 (Subtrochanteric fracture).

Statistical methods

All analyses are made using the primary data from the different cohorts. When investigating associations between risk factors and fracture or death from primary data, the relationships between risk factors and BMD could be explored. The use of primary data also lessens the risk of publication bias.

This method allows the estimation of the association between risk factors and fracture or death to be estimated in relation to each other

The estimated hazard functions for fracture and death were of the form exp(β_0 + β_1 ·time since assessment + β_2 ·age + β_3 ·Risk factor + β_4 ·BMD). They were estimated as continuous functions by Poisson regression [2 69].

The risk of fracture was estimated by Poisson regression model applied to each cohort and sex separately. Covariates always included time since start of follow up and current age. BMD was additionally excluded from the model. A further model included the interaction term between risk factor and age (β_k ·Risk factor·age), the interaction term between risk factor and time (β_k ·Risk factor·time) or the interaction with the risk factor itself (β_k ·Risk factor^2), the latter was done just for the continuous variables. Results of each cohort and the two sexes were weighted according to the variance and merged to determine the weighted mean and standard deviations.

Each variable that could be a candidate to be a risk factor was examined in the eleven cohorts. The ϐ-coefficients from the different cohorts were merged together as describe above. When a risk factor was absent in one cohort, the ϐ-coefficients for the other risk factors were treated as if the cohort had information on all risk factors. This could be done since the influence on the ϐ-coefficient of a risk variable, which has a non-dominating effect on the risk, is small. Only BMD has a dominating effect in this context. The factors that had a significant relationship with the risk of fracture were used to develop a hazard function for the risk of fracture.

The relationship between probability and hazard functions were then used to calculate the 10-year probability or fracture for a combination of the risk factors. Let h(t) denote the fracture hazard function, d(t) the death hazard function and g(t) the hazard function of the combined event hip fracture or death. Though the functions in typical applications contain several variables, only a time variable is given in order to simplify the notations. The hazard function g of having the first event of death or hip fracture is well approximated by d + h. From the general and well-known relationship between survival and hazard functions it is known that the probability of being free from any of the two types of events at the end of the period (0,t) is

$\exp(-\int_0^t g(u)du)$. The probability p of a hip fracture event before t is therefore given by

$$p = \int_0^t h(v)\exp(-\int_0^v g(u)du)dv \approx \int_0^t h(v)\exp(-\int_0^v (h(u)+d(u))du)dv .$$

When taking account of the hazard function of death in the calculation of 10 year probability, as showed above, the risk of death is taken account of twice, i.e. as a hazard function and also as a censoring factor when looking at the time to fracture when applying the Poisson model.

Four models were constructed from the risk factor analysis to compute fracture probabilities. These comprised the probability of hip fracture, with and without BMD, and the probability of other major osteoporotic fractures, with and without BMD. For each model, fracture and death as continuous hazard functions were computed using a Poisson regression as previously described. For each risk factor, all significant interactions terms that were identified by meta-analysis were entered (with age, time, sex and the risk factor) with and without BMD. Interactions that were significant for hip fracture risk were also entered into the model for other osteoporotic fractures, and also included in the model for death. Where interactions noted in the ñmega-analysesò were no longer significant for both hip fracture and other osteoporotic fractures, these were omitted in a step-wise manner by dropping the interaction with the largest p value. For the death hazard, all significant interactions for fracture risk were included and thereafter omitted if appropriate in a step-wise manner, as described for the fracture hazard.

The hazard functions given above were estimated by use of the eleven cohorts. If it is assumed that the relative importance of the risk variables is the same for all countries, e.g., we can use hazard functions of the form

$\exp(\beta_1 \times \text{time since assessment} + \beta_i \cdot \text{risk factor}_i) \cdot z(\text{age}) \cdot$ hazard function of Sweden,

where z(age) is a factor depending on age equal to $1/ E[\exp(\beta_i \times \text{risk factor}_i) \mid \text{age}]$, i.e. 1 divided by the conditional expected value of $\exp(\beta_i \times \text{risk factor}_i)$ given the value of age. If a random variable Y has a normal distribution with the mean μ and standard deviation σ then

$E[\exp(Y)] = \exp(\mu+\sigma^2/2)$. Denote $Y = \beta_1$ time since assessment + β_i Ārisk factor$_i$. By linear regression (in the simplest case) we determine $E[Y \mid \text{age}] = a + b \cdot \text{age}$ and the standard deviation σ around the regression line. Then z(age) can be put equal to $1/\exp(a + b \cdot \text{age} + \sigma^2/2)$.

Poisson regression models were also used to explore the relationships between mortality and BMD, mortality and Vitamin D plus fracture risk and adiponectin. A spline Poisson regression model was fitted using knots at certain percentiles points of BMD, vitamin D and adiponectin. The interaction between time since baseline and the risk variable studied was also used to elucidate the state of the relationship in both a linear (adiponectin) and non-linear shape.

Results

I and II: FRAX

For calculating the 10 year probability of fracture, the 11 cohorts, described in table 1 were used.

Table 1. Details of cohorts studied by meta-analysis of risk factors.

Cohort	Sample size	Person-years	Mean age (years)	Age range (years)	% female	Fracture history %	Any fracture	Osteoporotic fracture	Hip fracture
EVOS	13366	40160	63.8	41-91	52	36	715	715	44
OFELY	426	2124	64.2	50-89	100	16	53	-	-
CaMos	9400	26653	62.1	25-103	69	44	586	316	42
Rochester	1001	6228	56.8	21-94	65	18	289	244	42
Sheffield	2147	6826	80.0	74-96	100	51	284	236	62
Rotterdam	7774	43606	70.3	55-106	61	14	992	768	284
Kuopio	11798	56602	52.3	47-57	100	17	1053	-	-
Gothenburg I	2375	16439	78.8	69-86	61	9	431	431	336
Gothenburg II	7098	29750	58.9	21-89	100	18	441	312	29
DOES	2163	16333	70.7	57-96	61	15	532	418	107
Hiroshima	2613	9861	65.1	47-95	70	26	187	90	32
Totals	60161	254582	62.9	21-106	75	26	5563	3530	978

As a start a list was made of candidate risk factors, factors that possibly could have importance for the risk of fracture. Table 2 shows the factors that were listed. These risk factors and follow up for fracture and death were asked for in the eleven cohorts.

Then the cohorts and the statistical methods described in Methods were used when the list of risk factors were worked through.

Table 2. Potential risk factors

Age	Milk intake	Mental status
Height	BMD	Age at menopause
Weight	Ultrasound	HRT use
BMI	Bone markers	Oral contraceptive
Previous fracture	Glucocorticoids	Hysterectomy
Maternal history of fracture	Rheumatoid arthritis	Oopherectomy
Paternal history of fracture	Stroke	Neuromuscular data
Sibling history of fracture	Diabetes	Liability to fall
Smoking	Hyperthyroidism	
Alcohol use	Osteoarthritis	

Some risk factors were too heterogeneous in construct between cohorts; examples were mental status, neuromuscular data and liability to fall. For instance there were three cohorts that had some information on neuromuscular risk factors. For one cohort it was a question about multiple sclerosis or Parkinson disease, in another it was only on Parkinson disease and for the third it was the score from Rose Questionnaire. These three potential risk factors are just analysed for each cohort and the results were not merged. The conclusion was that there were not enough data and too heterogeneous to consider as a risk factor for fracture.

For some risk factors the results were merged, but they had no significant importance for fracture. Table 3 shows the hazard ratios with 95% confidence interval for the risk factors that were not significantly associated with fracture. For brevity, the hazard ratios for hip fracture are shown in Table 3, though the outcome of any fracture and osteoporotic fracture was also assessed (and also non-significant). Men and women were also analysed separately though the data are not shown. The number of individuals contributing to each hazard ratio differs since, for example, there were 10 cohorts that had information on menopause but there were 4 cohorts that had information on oral contraceptives. From the material available, it was concluded that there was no evidence that these risk variables had any significant importance for fracture.

Table 3. Factors that didnôt have significant importance for risk of hip fracture. Hazard ratios for men and women together (not adjusted for BMD).

	HR	95% CI
Low milk intake	1.17[a]	0.91-1.50
Age at menopause	1.00[b]	0.99-1.02
HRT use	1.32[c]	0.93-1.87
Oral contraceptives	0.86[c]	0.52-1.41
Hysterectomy	1.08[d]	0.86-1.36
Oopherectomy	1.01[d]	0.69-1.49

[a] Less than 1 glass per day

[b] per year change in age

[c] users versus non-users

[d] having the condition versus not

Secondary osteoporosis. Apart from the use of glucocorticoids, the prevalence of secondary causes of osteoporosis is low in population-based cohorts. In addition, few cohorts had information on secondary osteoporosis. For instance, 3 cohorts had information on rheumatoid arthritis and 5 cohorts had information on stroke. The information available is summarised in Table 4 for hip fracture risk. The outcome of any fracture and osteoporotic fracture was also assessed. Rheumatoid arthritis was taken as a surrogate for secondary osteoporosis, since it was the only factor that has significant importance for fracture. For any fracture it was a significant factor (HR=1.45; 95% CI= 1.16-1.80) and for osteoporotic fracture (1.56; 1.20-2.02). The risk persisted after adjusting for glucocorticoid use and prior fracture. The hazard ratio was lower but still significant after adjusting for BMD.

Biochemical markers of bone turnover (bone markers). There are situations where enough data could not be found. One example is bone markers. Data were available from 4 cohorts. Only one of them had data for men. Table 5 shows the hazard ratios for women. It is seen that resorption markers were of significant importance for hip fracture for women. When adjusted for BMD, the hazard ratio was 1.39 (1.10-1.77). These data, undertaken on a collection of markers, indicate the potential importance of resorption markers for fracture risk assessment but the data are too few in an international perspective to consider their inclusion in FRAX. Notwithstanding, this is an important area for future research.

Table 4. Secondary osteoporosis. Hazard ratios for hip fracture for men and women together (not adjusted for BMD).

	HR[a]	95% CI
Rheumatoid arthritis	1.95	1.11-3.42
Stroke	1.20	0.78-1.84
Diabetes	1.22	0.88-1.69
Hyperthyroidism	1.12	0.48-2.61
Osteoartritis	0.76	0.57-1.02

[a] having the condition versus not

Table 5. Bone markers. Hazard ratios for hip fracture for women together (not adjusted for BMD).

	HR[a]	95% CI
Resorption markers	1.62	1.28-2.04
Formation markers	1.15	0.73-1.81

[a] highest quartile versus the rest

Quantitative ultrasound (QUS) and Peripheral BMD. The most widely evaluated assessments are broad-band ultrasound attenuation (BUA) and speed of sound (SoS) (or ultrasound velocity) at the heel. There were only 2 cohorts having data on QUS. No cohort had data for men. Table 6 shows that BUA and SoS is of significant importance for the risk of hip fracture in women. For the outcome of any fracture and osteoporotic fracture there were data from just one cohort. Thus, QUS is also a potential technique that provides information on fracture risk for the research agenda rather than for its incorporation in FRAX.

There were three cohorts with information on peripheral BMD. All measurements were from the forearm. There was only one cohort in which there were data for men. Table 6 shows that peripheral BMD is of significant importance for the risk of hip fracture in women.

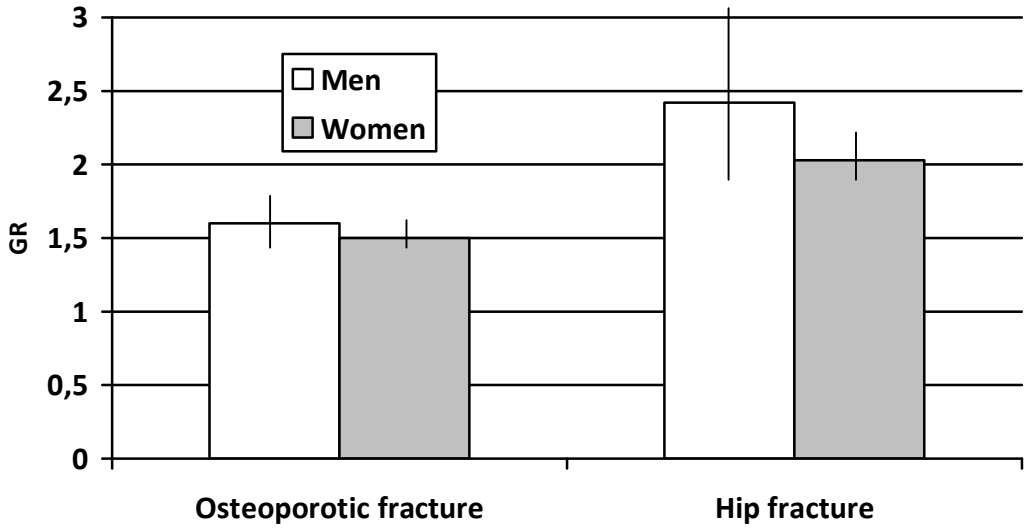
*Femoral neck BMD***.** Femoral neck BMD was available in all but two cohorts. Figure 1 shows the hazard ratios per 1 standard deviation change in BMD. There were no significant difference between men and women. Thus, the data for men and women were merged. The combined hazard ratio for men plus women for hip fracture was 2.18 (2.01-2.38) and for osteoporotic fracture was 1.55 (1.48-1.63) [70].

Table 6. Ultrasound and peripheral BMD. Hazard ratios for hip fracture for women together (not adjusted for BMD at femoral neck).

	HR[a]	95% CI
BUA	1.74	1.53-1.97
SoS	1.50	1.31-1.70
Peripheral BMD	1.30	1.15-1.48

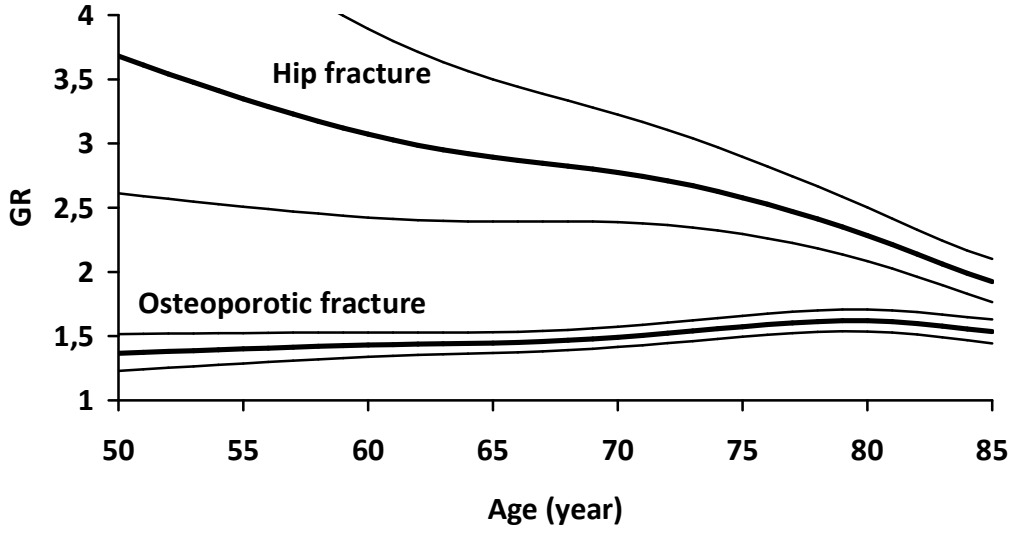
[a] per 1 standard deviation change

Figure 1: Gradient of risk (hazard ratio per 1 SD decrease) for femoral neck BMD for osteoporotic and hip fracture. The 95% confidence intervals are shown by the vertical lines.



*BMD and age***.** The effect of BMD on fracture risk was dependent on age. For osteoporotic fracture there was an increase of risk with increasing age, as shown in Figure 2 for men and women combined. At the age of 50 years the hazard ratio was 1.37 (1.23-1.52) and at the age of 80 it increased significantly to 1.62 (1.54-1.71). For hip fracture, the opposite pertained in that the gradient of risk decreased with increasing age. At the age of 50 years, the hazard ratio was 3.68 (2.61-5.19) and at the age of 80 years was 2.28 (2.09-2.50). The decrease in GR with age was also significant.

Figure 2: Gradient of risk (RR/SD) for fracture for the interaction with age (thin lines - 95% confidence interval)



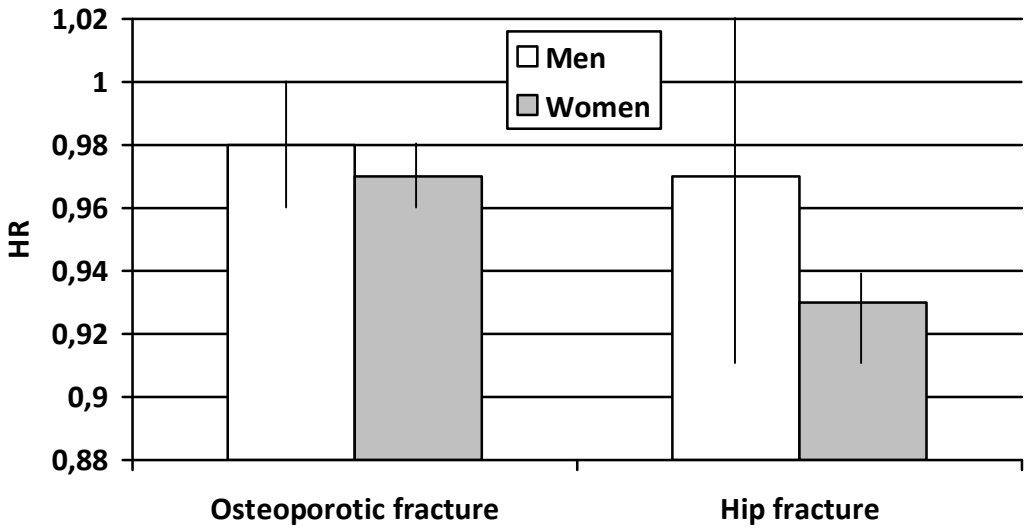
*BMD and BMD***.** For osteoporotic fracture (and any fracture) there was a higher gradient of risk the lower the BMD. This effect was significant. At a Z-score of ï 4 the hazard ratio was 2.10 per SD (1.63-2.71) and at a Z-score of ï 1 the risk was 1.73 per SD (1.59-1.89). A similar but less pronounced and non-significant effect was observed for hip fractures.

Thus, BMD is a risk factor for fracture of substantial importance and is similar on both sexes. Its use should, however, take account of the variations in predictive value with age and BMD.

Weight, height and BMI. Analysis were done of all three factors. Weight and BMI had almost the same results but height was rather weak as a risk factor for fracture . In addition, average body weight was variable between cohorts. These problems were reduced somewhat by the use of BMI which was chosen, therefore for further analysis.

BMI. All cohorts had data on BMI. Figure 3 shows the hazard ratios per unit increase in BMI. There were no significant difference between men and women. Thus men and women can be merged and the overall hazard ratio for men and women combined for hip fracture was 0.93 (0.91-0.94). For osteoporotic fracture it was 0.97 (0.96-0.98). After adjusting for BMD these hazard ratios became 1.00 (0.99-1.01) for osteoporotic fracture and 0.98 (0.96-0.99) for hip fracture [71]. Thus low BMI provides a risk factor for fracture, but in the presence of information on BMD, low BMI no longer contributed to facture risk.

Figure 3: Hazard ratio per unit increase for BMI for osteoporotic and hip fracture. The 95% confidence intervals are showed with the vertical lines. Not adjusted for BMD.



BMI and age. However the effect of BMI on fracture was dependent on age (Figure 4). For osteoporotic fracture there was a significant increase in the gradient of risk with increasing age, meaning that the hazard ratio for fracture was more pronounced the older the individual. In contrast, for hip fracture the gradient of risk decreased with increasing age, although this trend was not significant. Overall, the pattern of the relationship between BMI and age was similar to that observed for BMD (see Figure 2).

BMI and BMI. The contribution of BMI to fracture risk was much more marked at low values of BMI than at values above the median (Figure 5). This non-linear relation of risk with BMI was most marked for hip fracture risk. Thus, low BMI constitutes a risk factor for fracture to an extent much greater than high BMI protecting against fracture. These data show that there is no conflict between advice for weight control for the prevention of diabetes or cardiovascular disease, and that for the prevention of osteoporotic fractures.

In summary, low BMI confers a risk of fracture of substantial importance that is largely independent of sex, but dependent on age and BMD. The significance of BMI as a risk factor varies according to the level of BMI.

Figure 4: Hazard ratio per 1 unit increase for BMI for fracture for the interaction with age in men and women combined (thin lines - 95% confidence interval)

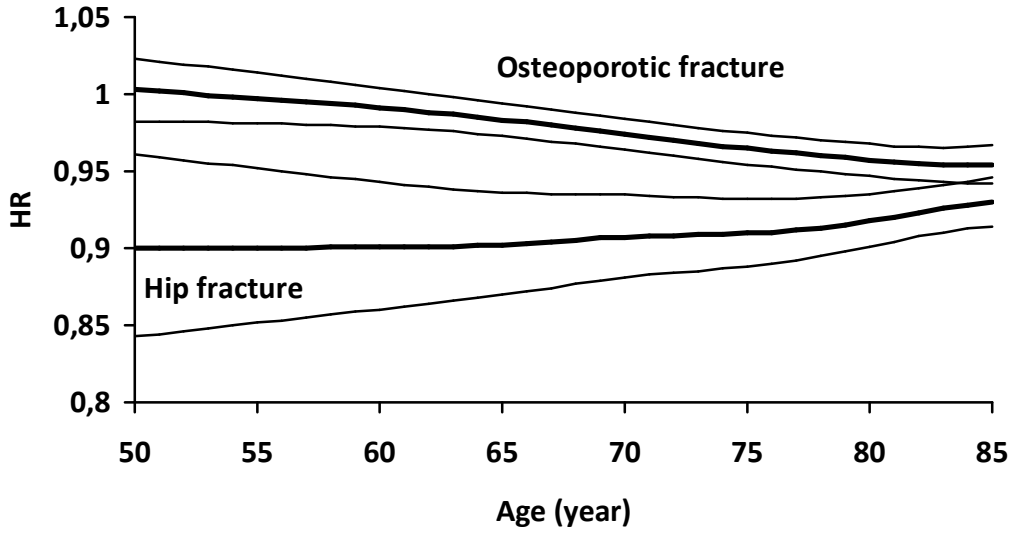
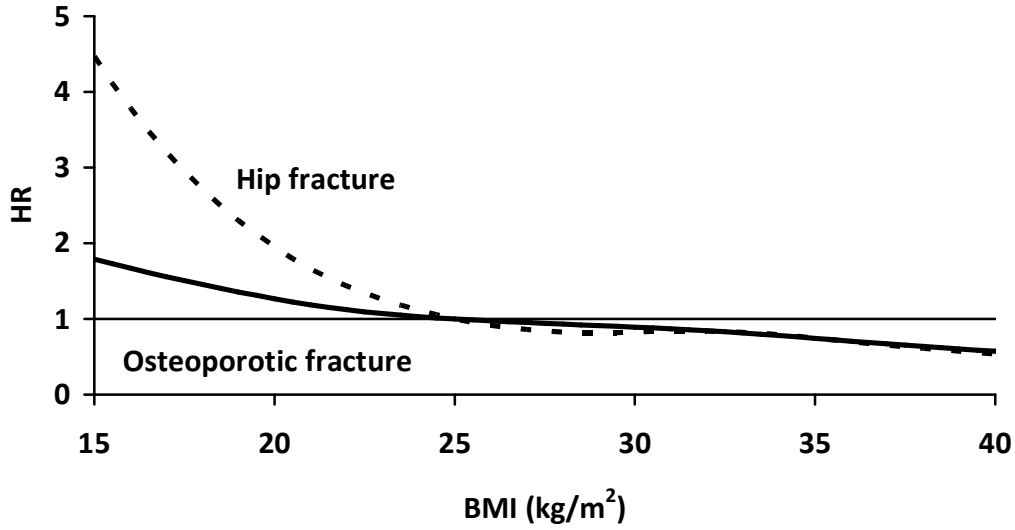


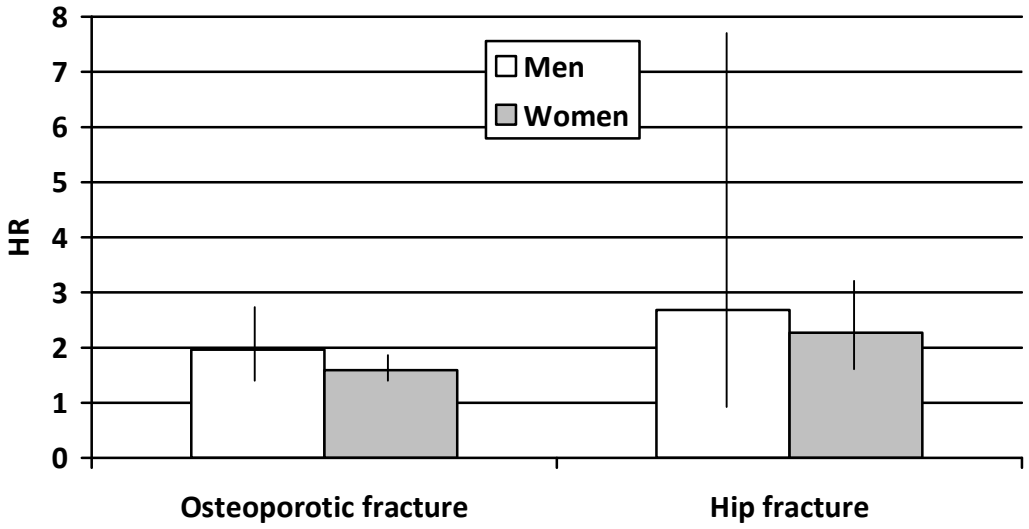
Figure 5: Hazard ratio versus 25 kg/m^2 for fracture for the interaction with BMI



Ever use of oral glucocorticoids. Previous glucocorticoid use was associated with a significantly increased risk of osteoporotic fracture and hip fracture (Figure 6). There was no significant difference in risk between men and women. Thus data for men and women were merged and the overall hazard ratio of ever use of glucocorticoids versus non-users was 1.65 (1.42-1.90) for osteoporotic fracture and 2.31 (1.67-3.20) for hip fracture. The estimate of

relative risk was higher at younger ages but not significantly so. The risk was marginally and not significantly downward adjusted when BMD was included in the model. The risk was independent of prior fracture [72].

Figure 6: Hazard ratio for ever use of glucocorticoids for osteoporotic and hip fracture. The 95% confidence intervals are showed with the vertical lines. Not adjusted for BMD.

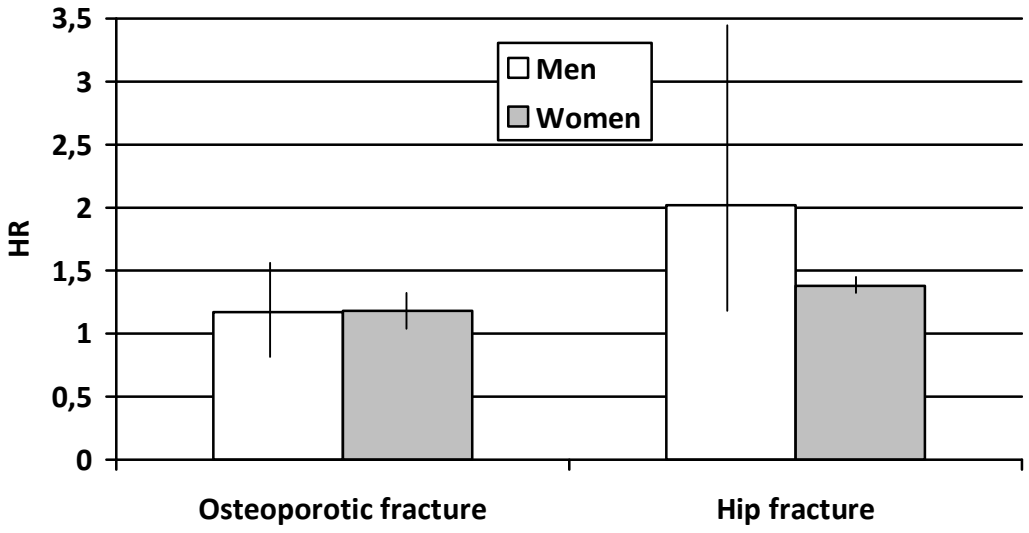


Thus, prior and current exposure to glucocorticoids confers an increased risk of fracture that is of substantial importance beyond that explained by the measurement of BMD. The effect was independent of age, sex and previous fracture.

Maternal, paternal and sibling history. Data were available for a family history in either parent and in siblings and each were analysed separately and in different combinations. In addition data were available for a family history of hip fracture or any osteoporotic fracture. When maternal, paternal and sibling history was combined, hazard ratios were marginally higher, but similar to the combination of maternal or paternal history alone. A parental history was chosen as the index variable since the probability of a sibling varies markedly around the world and is less appropriate, therefore, for use in an international context.
Maternal or Paternal history. A parental history of any fracture was associated with a significantly increased risk of osteoporotic fracture and hip fracture (Figure 7). No significant difference in risk was seen between men and women so that the data for men and women were merged. The overall hazard ratio for osteoporotic fracture was 1.18 (1.06-1.31) and for

hip fracture 1.49 (1.17-1.89). The hazard ratio was higher at younger ages but not significantly so. When the risk variable was confined to a parental history of hip fracture (rather than any fracture), the hazard ratio was larger. A family history of hip fracture in parents was associated with a significant risk of osteoporotic fracture 1.54 (1.25-1.88) and hip fracture 2.27 (1.47-3.49). The risk was not significantly changed when BMD was added to the model [73].

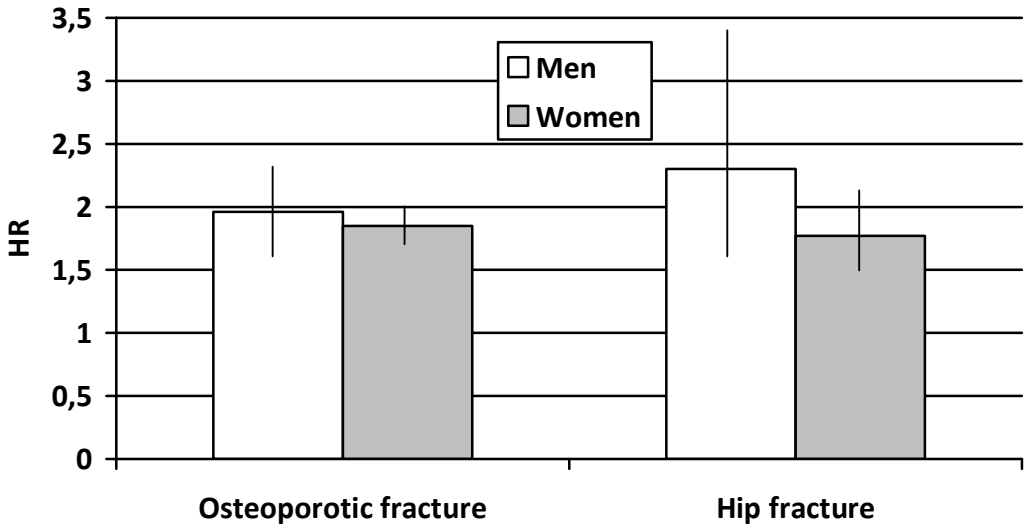
Figure 7: Hazard ratio for parental history of any fracture for osteoporotic and hip fracture. The 95% confidence intervals are showed with the vertical lines. Not adjusted for BMD.



Thus, a parental history of fracture (particularly a family history of hip fracture) confers an increased risk of fracture that is independent of BMD. The effect is independent of age and sex.

Previous fracture. A previous fracture history was associated with a significantly increased risk of fracture (Figure 8). There was no significant difference in hazard ratio between men and women and the data for men and women were merged. The hazard ratio for osteoporotic fracture was 1.86 (1.72-2.01) and for hip fracture was 1.85 (1.58-2.17). The hazard ratio was marginally downward adjusted when account was taken of BMD. The hazard ratio was stable with age except in the case of hip fracture where the hazard ratio decreased significantly with advancing age, from 5.04 (2.66-9.56) at 50 years of age to 1.90 (1.58-2.28) at the age of 80 years [74].

Figure 8: Hazard ratio for previous fracture for osteoporotic and hip fracture. The 95% confidence intervals are showed with the vertical lines. Not adjusted for BMD.

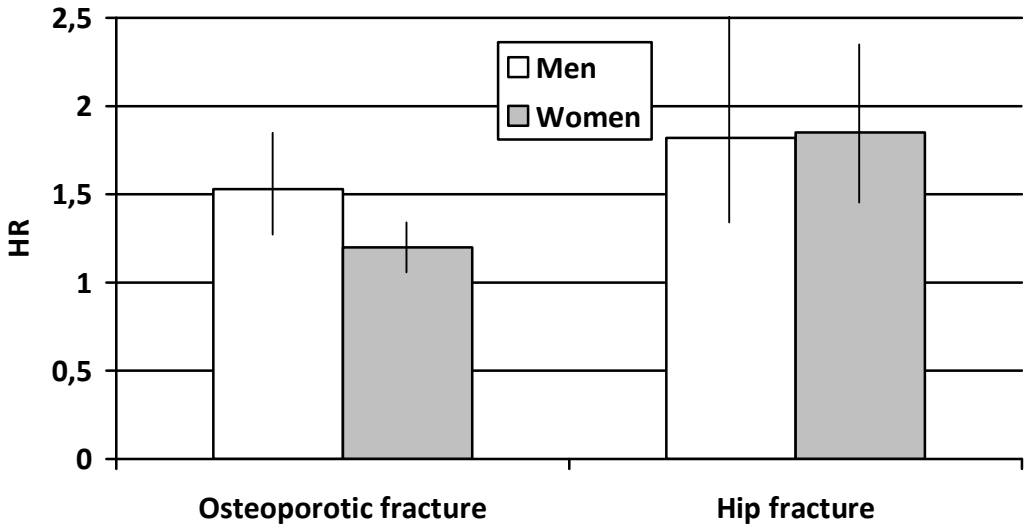


In conclusion, a previous history of fracture confers an increased risk of fracture of substantial importance beyond that explained by measurement of BMD. The effect is dependent of age and independent of sex.

Current smoking. Data were available for both current smoking and ever smoking. The hazard ratios were higher for current smoking than ever smoking. Current smoking was associated with a significantly increased risk of fracture compared to non-smokers (Figure 9). Hazard ratios were significantly higher in men than in women for all fractures and for osteoporotic fractures, but not for hip fracture. Hazard ratio was marginally downward adjusted when account was taken of BMD but remained significantly increased. For osteoporotic fracture, the hazard ratio increased with age, but decreased with age for hip fracture. None of these effects were significant ($p>0.30$)[75].

Thus, current smoking is associated with a significantly increased risk of fracture compared with non-smokers. The effect is dependent of sex and independent of age.

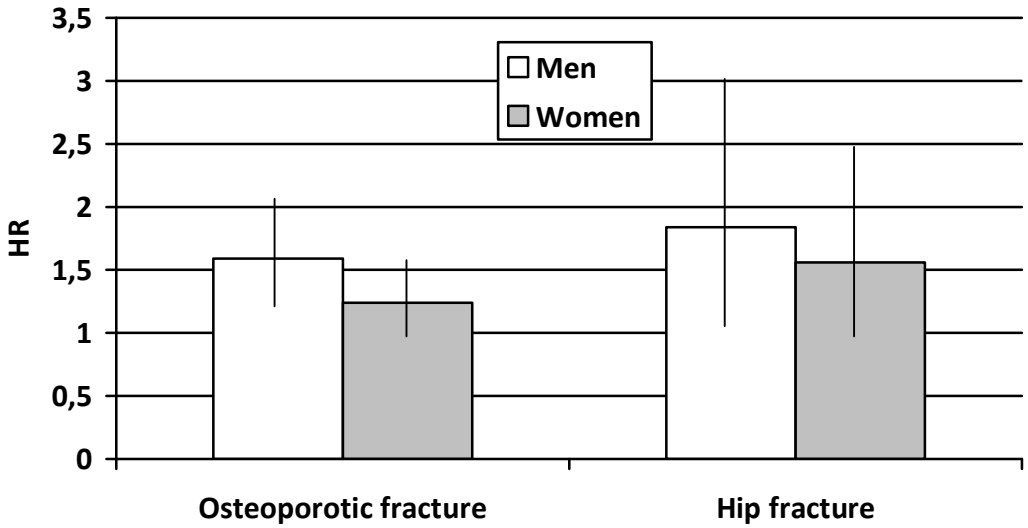
Figure 9: Hazard ratio for current smoking for osteoporotic and hip fracture. The 95% confidence intervals are showed with the vertical lines. Not adjusted for BMD.



Alcohol intake. The last risk factor to be handled was alcohol intake. The unit is average units of consumption per day. A unit of alcohol is equivalent to 8g in the UK, though varies somewhat in different countries. When alcohol intake was considered as a continuous variable, there was no significant increase in risk observed at intakes of 2 units or less daily. For this reason, intake of alcohol was dichotomised using a cut off of 3 or more units per day (Figure 10). High intake of alcohol, defined in this way, was associated with a significant increase in osteoporotic and hip fracture risk. Hazard ratios were moderately but not significantly higher in men than in women and the data for men and women were merged. The overall hazard ratio for those drinking more than 2 units per day versus those who did not was 1.38 (1.16-1.65) for osteoporotic fracture is and 1.68 (1.19-2.36) for hip fracture. There was no significant interaction with age or with BMD [76].

Thus, reported intake of alcohol confers a risk of some importance beyond that explained by BMD. The effect is independent of age and sex.

Figure 10: Hazard ratio for alcohol intake >2 units per day for osteoporotic and hip fracture. The 95% confidence intervals are showed with the vertical lines. Not adjusted for BMD.



Risk factors for fracture. It is concluded that the risk factors detailed above confer risks of importance beyond that explained by BMD. An exception is BMI. Their validation on an international basis permits their use in case finding strategies. The following risk factors were selected on the basis of their international validity and the ease with which the risk factor could be utilised in clinical practice.

- BMD at femoral neck
- BMI
- Glucocorticoid exposure
- Family history
- Previous fracture
- Smoking
- Alcohol intake
- Secondary osteoporosis

Interactions. Interactions between the risk variables were investigated. Our findings are summarized in table 7.

Table 7. Significant interactions determined from meta-analyses of risk factors for hip fracture (HF) or any osteoporotic fracture (OPF).

	BMD		Age		Variable*		Sex		Time	
Risk factor	HF	OPF	HF	OPF	HF	OPF	HF	OPF	HF	OPF
BMI	-	-	-	+	+	-	-	-	+	-
Prior fracture	-	-	+	-			-	-	-	-
Glucocorticoids	-	-	-	-			-	-	-	-
Family history	_	_	-	-			-	-	-	-
Smoking	-	-	-	-			-	-	-	-
Rheumatoid arthritis	-	-	-	-			-	-	-	-
Alcohol	-	-	-	-			-	-	-	-
BMD			+	+	-	+	-	-	-	-

- denotes no effect ($p>0.05$); + denotes a significant interaction.

* denotes an interaction of the variable with the variable, e.g. BMI·BMI.

Table 8 shows the risk variables are present in the different cohorts used to construct the FRAX models

To calculate the 10 year probability of hip and osteoporotic fracture six hazard functions are needed. These were estimated by Poisson regression. The six hazard functions were

- for the risk of osteoporotic fracture without hip fracture without BMD in the model,
- for the risk of osteoporotic fracture without hip fracture with BMD in the model,
- for the risk of hip fracture without BMD in the model,
- for the risk of hip with BMD in the model,
- for the risk of death without BMD in the model
- for the risk of death with BMD in the model.

Those variables that did not have significant importance in the multivariable models were deleted. The final results are shown in table 9.

Table 8. Risk factors examined by cohort.

Cohort	BMI	Family history	BMD	Gluco-corticoids	Prior fracture	Smoking	Alcohol	Rheumatoid arthritis
EVOS/EPOS	+	+	+	+	+	+	-	-
CaMos	+	+	+	+	+	+	+	+
Rochester	+	+	+	+	+	+	-	-
Rotterdam	+	+	+	+	+	+	+	-
DOES	+	+	+	+	+	+	+	+
Gothenburg I	+	-	+	-	+	+	-	-
Gothenburg II	+	+	+	+	+	+	-	-
Hiroshima	+	-	+	+	+	+	-	-
Sheffield	+	+	+	+	+	+	-	+
Kuopio	+	-	+	-	+	+	-	-
OFELY	+	-	+	-	+	-	-	-

Table 9

Variables in the hazard function for fracture	Variables in the hazard function for death
Current time	Current time
Min(Current age, 65)	Min(Current age, 65)
Max (Current age-65,0)	Max (Current age-65,0)
Sex (1/2)	Sex (1/2)
Min (BMI, 25)	Min (BMI, 25)
Max (BMI-25,0)	Max (BMI-25,0)
Previous fracture (0/1)	Current smoke (0/1)
Mother/Father (0/1)	Glucocorticoids (0/1)
Current smoke (0/1)	Sex x current age
Glucocorticoids (0/1)	BMD
RA (0/1)	
Alcohol (0/1)	
Sex x current age	
Previous fracture x min(current age,80)	
Mother/Father x max(0,min(age-65,10))	
Min (BMD, 0)	
Max (BMD,0)	
BMD x current age	

The hazard functions were estimated by use of the eleven cohorts from different countries and the data calibrated to the epidemiology of a specific country. By considering all variables except age, a risk score was calculated by multiplying each variable by the corresponding beta coefficient and adding the products. A 10 year probability is then calculated.

Table 10 shows the ten-year probability fracture for men and women in Sweden.

Table 10. Ten-year probability of fracture (%) at the sites shown for men and women with a BMI of 24 kg/m^2 according to age and the presence or absence of a single risk factor in the absence of BMD.

	Osteoporotic fracture[a]				Hip fracture			
	50	60	70	80	50	60	70	80
(a) Men								
No clinical risk factors	3.3	5.1	7.8	12	0.3	0.8	2.8	7.1
Parental history of hip fracture	6.6	9.6	13	26	0.3	1.1	5.8	22
Current cigarette smoking	3.5	5.5	8.6	14	0.4	1.2	3.9	9.1
Alcohol intake >2 units daily	4.0	6.2	10	16	0.4	1.3	4.2	11
Rheumatoid arthritis	4.5	7.0	11	18	0.5	1.5	4.8	12
Oral glucocorticoids	5.4	8.2	12	18	0.6	1.7	5.2	12
Prior fragility fracture	7.2	10	15	19	1.0	2.4	5.8	11
(b) Women								
No clinical risk factors	4.1	7.6	14	26	0.4	1.3	4.7	13
Parental history of hip fracture	8.1	14	23	47	0.5	1.7	9.9	38
Current cigarette smoking	4.4	8.3	16	29	0.6	2.0	6.9	18
Alcohol intake >2 units daily	5.0	9.3	18	33	0.6	2.0	7.1	19
Rheumatoid arthritis	5.6	10	20	36	0.7	2.3	8.2	22
Oral glucocorticoids	6.8	13	23	38	0.9	2.8	9.6	23
Prior fragility fracture	9.0	15	26	39	1.6	3.8	9.8	20

[a]Clinical spine, hip, humeral or forearm fracture.

Table 11 shows the ten-year probability of having a fracture for men and women in Sweden.

Table 11. Ten-year probability of fracture (%) at the sites shown for men and women with a BMI of 24 kg/m^2 according to age and the BMD T-score, no clinical risk factors present.

	Osteoporotic fracture[a]				Hip fracture			
	50	60	70	80	50	60	70	80
(a) Men								
BMD T-score 0	3.2	4.3	5.3	6.2	0.2	0.4	0.9	2.1
BMD T-score -1	4.2	5.7	7.1	8.2	0.6	1.1	2.1	3.6
BMD T-score -2	6.6	8.9	11	12	2.2	3.2	4.8	6.5
BMD T-score -2.5	8.9	12	14	15	4.2	5.4	7.3	8.8
(b) Women								
BMD T-score 0	3.7	5.6	7.6	10	0.1	0.2	0.6	1.7
BMD T-score -1	4.3	6.7	9.8	14	0.4	0.7	1.6	3.6
BMD T-score -2	6.3	9.7	14	19	1.4	2.2	4.2	7.4
BMD T-score -2.5	8.1	12	18	24	2.7	4.0	6.8	11

[a]Clinical spine, hip, humeral or forearm fracture.

The 10 year probabilities are based on a risk score which was built as showed in table 8 (minus the coefficients for time and age). Table 12 shows the gradient of risk per SD change in score with the use of BMD, clinical risk factors or the combination. Note that the gradient of risk was age-dependent. For hip fracture risk, higher gradients if risk were observed in younger individuals, whereas the opposite pertained for the risk of other osteoporotic fracture.

Since the age distribution varied from cohort to cohort, the gradients of risk in individual cohorts were age-standardised. The index cohorts used to create FRAX were compared with information from the validation cohorts collected (Table 13). The performance of the risk score in the validation cohorts was similar to that found in the source cohorts.

Table 12. Gradients of risk per SD change in risk score (with 95% confidence interval) with the use of BMD, clinical risk factors or the combination.

	Gradient of risk		
Age	BMD only	Clinical risk factors alone	Clinical risk factors + BMD
(a) Hip fracture			
50	3.68 (2.61-5.19)	2.05 (1.58-2.65)	4.23 (3.12-5.73)
60	3.07 (2.42-3.89)	1.95 (1.63-2.33)	3.51 (2.85-4.33)
70	2.78 (2.39-3.23)	1.84 (1.65-2.05)	2.91 (2.56-3.31)
80	2.28 (2.09-2.50)	1.75 (1.62-1.90)	2.42 (2.18-2.69)
90	1.70 (1.50-1.93)	1.66 (1.47-1.87)	2.02 (1.71-2.38)
(b) Other osteoporotic fractures			
50	1.19(1.05-1.34)	1.41 (1.28-1.56)	1.44 (1.30-1.59)
60	1.28 (1.18-1.39)	1.48 (1.39-1.58)	1.52 (1.42-1.62)
70	1.39 (1.30-1.48)	1.55 1.48-1.62)	1.61 (1.54-1.68)
80	1.54 (1.44-1.65)	1.63 (1.54-1.72)	1.71 (1.62-1.80)
90	1.56 (1.40-1.75)	1.72 (1.58-1.88)	1.81 (1.67-1.97)

Table 13. Gradient of risk of original and validation cohorts standardised to the age of 70 years. 95% confidence intervals are shown in parentheses.

	Hip fractures		Other osteoporotic fractures	
Cohort	without BMD	with BMD	without BMD	with BMD
Geelong I	1.88 (1.07-3.29)	1.71 (0.74-3.96)	1.34 (1.12-1.61)	1.57 (1.31-1.88)
Geelong II	1.50 (1.05-2.13)	3.40 (1.99-5.80)	1.30 (1.14-1.48)	1.54 (1.36-1.76)
OPUS	2.48 (1.26-4.91)	2.09 (0.98-4.47)	1.32 (1.08-1.62)	1.38 (1.15-1.65)
York	2.05 (1.13-3.72)	- (-)	1.74 (1.37-2.21)	- (-)
PERF	1.28 (1.01-1.62)	2.72 (1.43-5.16)	1.14 (1.05-1.23)	1.19 (1.05-1.35)
SOF	1.58 (1.34-1.87)	2.21 (1.79-2.73)	1.24 (1.15-1.34)	1.31 (1.20-1.42)
THIN	1.54 (1.45-1.63)	- (-)	1.29 (1.26-1.32)	- (-)
EPIDOS	1.70 (1.18-2.44)	2.89 (1.98-4.21)	1.41 (1.11-1.78)	1.47 (1.17-1.86)
Miyama	2.87 (0.98-8.37)	3.07 (0.97-9.64)	3.50 (2.42-5.07)	2.80 (2.06-3.80)
SEMOF	1.76 (1.03-3.01)	2.18 (1.27-3.74)	1.32 (1.10-1.58)	1.44 (1.16-1.79)
WHI	1.54 (1.43-1.66)	2.44 (1.85-3.21)	1.26 (1.23-1.29)	1.46 (1.35-1.58)
Original cohorts	1.84 (1.65-2.05)	2.91 (2.56-3.31)	1.55 (1.48-1.62)	1.61 (1.54-1.68)

III: BMD ï death

The principal aim of paper III was to examine the relationship between BMD and death in men. Standardised BMD at all sites was significantly lower in men who subsequently died compared with men who remained alive during the follow-up. The hazard ratio for 1standard deviation decrease in total hip BMD (GR) was 1.28 (95% CI 1.15-1.43) , adjusted for age and time since baseline and 1.27 (95% CI 1.14-1.42) when adjusted for age, time since baseline, cancer, angina, diabetes, systolic blood pressure and general health.

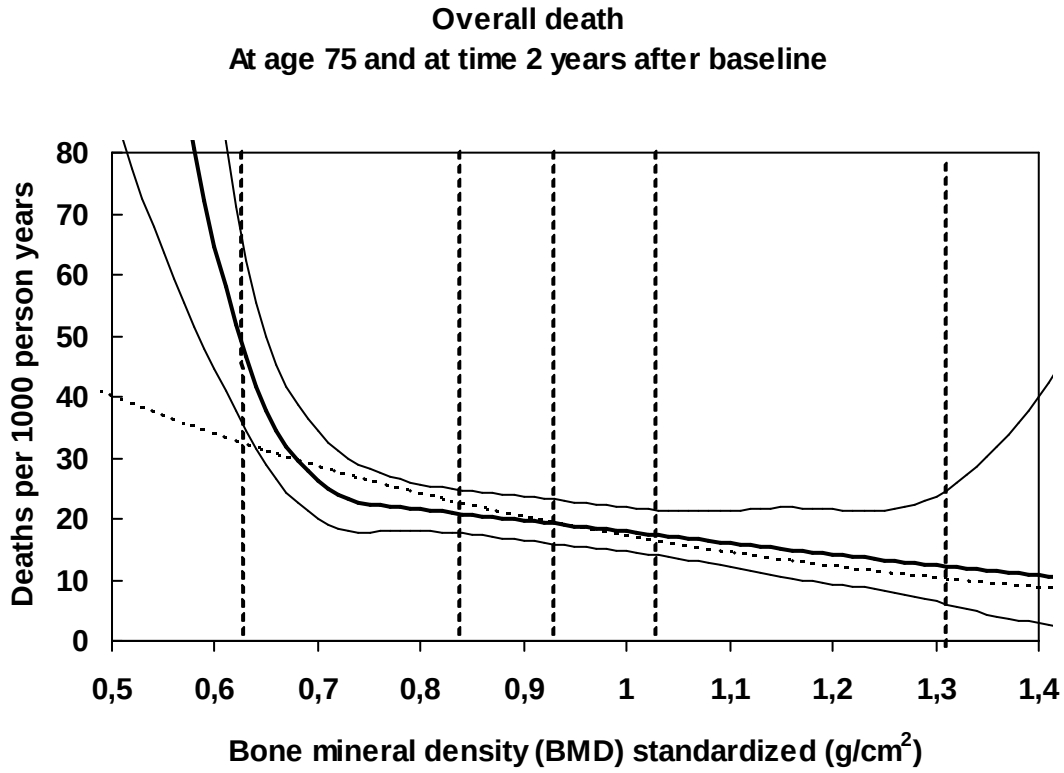
The relation between BMD and death was, however more complex than a simple gradient of risk. In figure 11 the dashed diagonal line describes the relation found between death and total hip BMD when it was assumed that there is a constant gradient of risk of 1.27 all over the observed range of BMD. The bold line describes the relationship when the hazard function is described with spline functions (knots in the 1^{st}, 10^{th}, 90^{th} and 99^{th} percentiles of BMD). There was a significant difference between the slope of the spline function below and above the 25^{th} percentile (p=0.020).

IV: Vitamin D

There are some analogies to be drawn from the study of BMD and death and the findings in paper IV in that a non-linear relation was established between serum 25(OH)D and the risk of death. Serum 25(OH)D was significantly lower in men who subsequently died compared with men who remained alive during the follow-up. The hazard ratio for a 1SD decrease in 25(OH)D (GR) was 1.16 (95% CI 1.07-1.26), adjusted for age and time since baseline. When adjusted for age, time since baseline, total hip BMD, cancer, angina, diabetes, outdoor activity, physical activity, number of medication and general health the GR was 1.06 (95% CI 0.98-1.16).

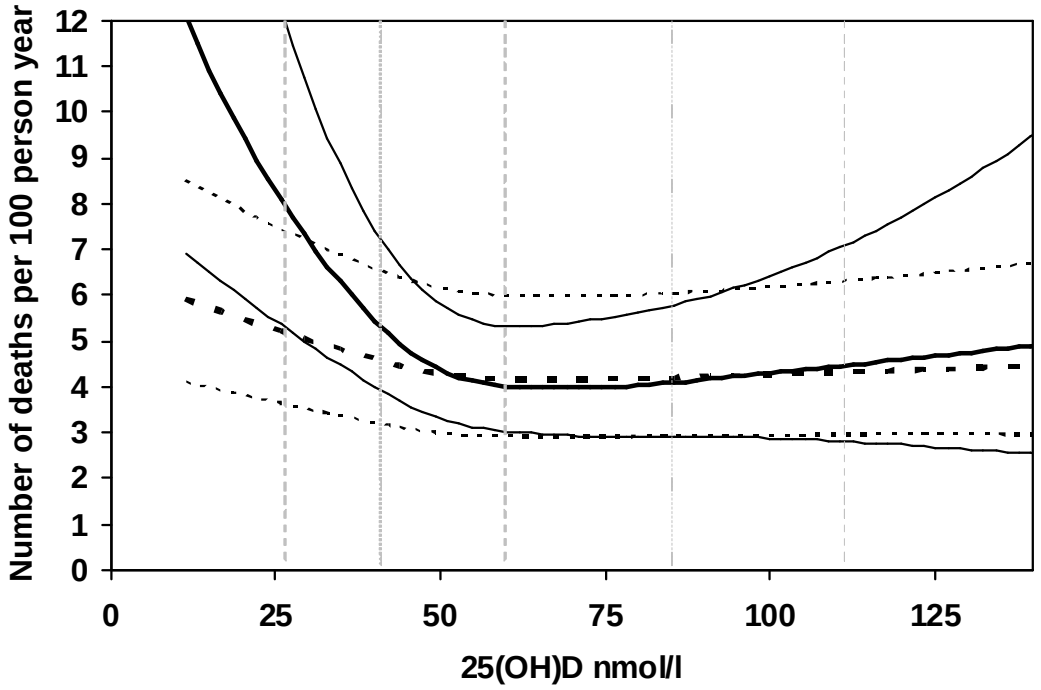
As was the case for BMD and death, increased mortality was confined to low values of the risk variable (Figure 12). When comparing the fit of the models with and without allowing for non-linearity (and interaction with time- see below), the former had a significantly better fit using the maximum-likelihood test (p=0.0015). Thus, the mortality hazard was not increased above values of 60-75 nmol/l of 25(OH)D (threshold dependent on the model used).

Figure 11 The hazard function of death (momentary risk) and 95% confidence interval depending on total hip BMD for a man aged 75 years after 2 years from baseline, with no history of cancer, angina or diabetes and with an average systolic blood pressure and self-estimated general health. The dashed diagonal line represents the relationship assuming that the gradient of risk is the same all over the whole range of BMD. The vertical dashed lines in the figure represent the 1st, 25th, 50th, 75th and the 99th percentiles.



Over and above this appearance of a threshold effect, the impact of low 25(OH)D values appeared to attenuate with time. The maximum effect of vitamin D on mortality was at 3.25 years after baseline. Figure 12 shows the death risk per 100 person years for different values of 25(OH)D at 3 years of follow up and at 6 years since baseline. The relationship between mortality and 25(OH)D was described with spline functions with knots in 10th, 50th and 90th percentiles.

Figure 12. The hazard function of death (momentary risk) and 95% confidence intervals according to serum 25(OH)D for a man aged 75 years after 3 years of follow up (continuous lines) after 6 years of follow up (dotted lines). Diabetes is set to no like outdoor activity. Physical activity, BMD and general health is set to average value of the cohort. The vertical dashed lines in the figure represent the 1st, 10th, 50th, 90th and 99th percentiles.



V: Adiponectin

The Mr Os cohort was also used to examine a novel potential index of fracture risk in serum adiponectin. At the time of the analysis, the 999 men aged 70-81 years had been followed for up to 7.4 years, with an average follow up of 5.2 years. Of these, 150 men had a fracture during follow up. Adiponectin was significantly lower in men who subsequently fractured compared with men who did not fracture during the follow-up. The hazard ratio for 1standard deviation increase in adiponectin (GR) was 1.44 (95% CI 1.27-1.64), adjusted for age and time since baseline and 1.32 (95% CI 1.15-1.52) adjusted for age, time since baseline, BMD total hip, previous fracture and general health.

Figure 13 shows the relationship between adiponectin and fracture risk with spline functions (knots in 10th, 50th and 90th percentiles). Fracture risk increased with increasing values of

serum adiponectin but the association was not significant at values below 18 εg/ml. Above threshold value the GR was 1.59 (95% CI 1.23-2.05).

When the interaction between serum adiponectin and the time since baseline was entered in the Poisson model, the interaction was significant (p=0.020). The gradient of fracture risk per 1 SD (GR) decreased with time since baseline measurements (Figure 14).

Figure 13. The hazard function of fracture (momentary risk) assessed and 95% confidence intervals according to baseline serum adiponectin for a man where age was set to 75 years, the time since baseline was set to 2 years of follow up. Previous fracture was set to no and BMD and general health is set to the average value of the cohort. The vertical dashed lines in the figure represent the 1st, 10th, 50th, 90th and 99th percentile.

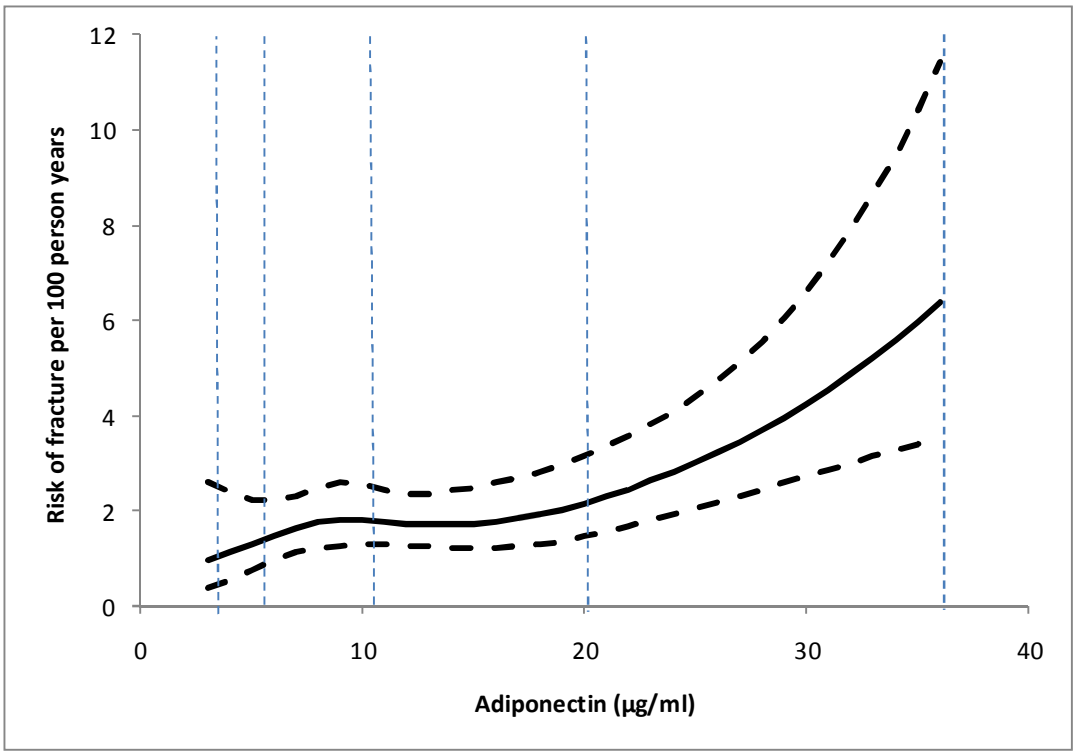
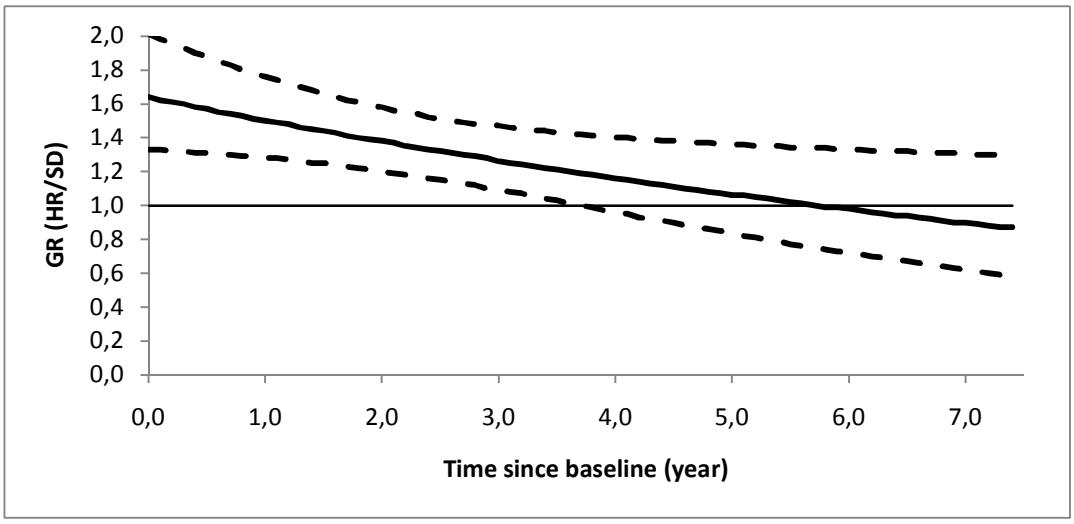


Figure 14. Gradient of risk per 1 SD (95% confidence interval) for the association between serum adiponectin and the risk of any fracture



Discussion

FRAX® I-II

Many risk factors for fracture are known and could be used to develop risk engines for fracture. FRAX® is an example of a risk engine for fracture that was developed with use of international population-based prospective cohorts.. The obvious application of FRAX® is in the assessment of individuals to identify patients suitable for pharmacological intervention and it has been widely used for this purpose. The web site, launched in 2008, currently receives about 200,000 hits per working day. Because of the ability of internet and computers the algorithms behind the risk engines donôt have to be simple. Following regulatory review by the US Food and Drug Administration, FRAX has been incorporated into DXA scanners to provide FRAX probabilities at the time of DXA scanning. FRAX is incorporated (or in the process) in many clinical guidelines [77-87] and has also been used for health economic calculations[88 89].

FRAX® has also been extensively validated [15 90-99]. There have been calls to add variables to FRAX® and of course that could be valuable if risk prediction can be shown to be improved. To add risk factors with the same scientific rigour as the current risk factors included in FRAX, will demand the study of several international prospective cohorts of normal populations including the new risk factor and the established risk factors. This is required to

investigate the interactions between all risk factors and their relation to time since baseline. Some authors suggest that FRAX® variously overestimates or underestimates fracture risk but in the light of the different fracture incidence within each country, both ethnic-specific differences[100-102] and differences between urban and rural communities[103-110] it would be surprising to find identical fracture hazards when regional cohorts are examined. For this reason, the finding of modest differences (up to two-fold) in expected and observed fracture rates from small cohorts should not be used to derive a conclusion that a FRAX model is not well calibrated, particularly if based on national fracture and mortality statistics.

The use of FRAX® with the generation of a number does not, however, replace clinical judgement. Several of the clinical risk factors identified take no account of dose-response, but give risk ratios for an average dose or exposure. By contrast, there is good evidence that the risk associated with excess alcohol consumption, cigarette smoking and the use of glucocorticoids is dose-responsive [75 76 109]. In addition, the risk of fracture increases progressively with the number of prior fractures [111 112]. These limitations should be recognised when interpreting the FRAX® result in the clinic. A guide for the effect of doses of glucocorticoids to FRAX® has been developed[113].

At present the FRAX® tool limits BMD to that measured at the femoral neck. This is because of the wealth of data available for this site. There are, however, other bone measurements that provide information on fracture risk. These include BMD at other skeletal sites [114], ultrasonography [115], quantitative computed tomography [116] and the biochemical indices of bone turnover. A guide for the effect of differences between lumbar spine BMD and femoral neck BMD to FRAX® has been developed[117].

For these reasons, the FRAX® tool should not be considered by physicians as a gold standard, but rather as a platform technology on which to build as new validated risk indicators become available. Notwithstanding, the present model provides an aid to enhance patient assessment by the integration of clinical risk factors alone and/or in combination with BMD.

III-V

One reason for investigating risk factors for fracture and death is that risk engines can be developed. To be able to make a good risk engine many aspects of the risk factor must be

examined, such as the risk factors dependence on time, age, other risk factors and if the association between the risk factor and the endpoint is different for different values of the risk factor (a non-linear association). For the association between BMD and mortality, a non-linear association was shown in elderly men. For the association between vitamin D and mortality, a non-linear association was also shown that also decreased in importance with the time since baseline measurement in elderly men. Additionally, the association between adiponectin and fracture risk was dependent on time since baseline measurement.

Our findings that the association between vitamin D and mortality and the association between adiponectin and fracture is dependent on time may explain, in part, the disparate conclusions reported in previous studies that have examined these relationships. Whereas the finding of a significant relationship is consistent with our results, so too is the absence of a significant effect, particularly after a longer follow up.

The most obvious limitation of these studies is that the cohort is limited to elderly men (70-80 years) and the relationships among women or men at other ages is not known. The participation rate was 45% and there is likely to be a healthy selection bias. A healthy volunteer bias is expected to converge with the general population over time, and evidence for such a bias are shown in the different models presented. This is a factor to be aware of when interpreting the result, but since ótime since baselineôis in the model, this effect was in part adjusted for. One strength of these studies is the detail of the baseline assessment so potential confounders can be examined and adjustment made where appropriate.

In conclusion, there are significant relationships between BMD and mortality, vitamin D and mortality and between adiponectin and fracture. The relationship between BMD and mortality and between vitamin D and mortality are both non-linear and the relationship between vitamin D and mortality is dependent on time since baseline. The relationship between adiponectin and fracture risk is also dependent on time. These data using advanced analytic techniques, suggest the increased risk of death is much greater at low values of measured BMD, at least in elderly men. If these findings were confirmed in other cohorts and in women, this would have marked implications for fracture risk assessment in that their accuracy could be improved by accommodating this non-linear relationship. This analysis also has important implications for the choice of risk variables that might be incorporated into future models. In selecting novel

risk factors, it will be important to determine their operating characteristics with the passage of time, particularly in models such as FRAX that use a 10 year time horizon

Conclusions

In conclusion, the findings in this thesis produced a detailed risk assessment tool for fracture (FRAX) which is unique in the field since it is based on international cohorts, externally validated and has taken death risk into account. The tool is however limited by the risk variables reported in the cohorts and could in the future be enhanced by inclusion of other risk variables in the hazard function for death and fracture. As a start of investigating new risk variables for men the thesis has investigated the association between BMD and death, vitamin D and death and adiponectin and fracture. Those risk variables could be important for the construct of a future risk assessment tool if cohorts are developed that including these risk variables and the clinical risk factors used in FRAX and BMD for men and women over a wider range of age.

Erratum:

Paper I:

- Reference 14 should be: Stenstrom M, Olsson J, Mellstrom D. Thyroid hormone replacement is not related to increased risk of osteoporosis. *Osteoporos Int* 2000;11(suppl 2):S144.

Paper II:

- In table 1 the names Gothenburg I and II should change places.
- Page 1042 right panel row 12 the formula should be $\exp([\log(2.8)^2 + \log(1.8)^2]^{1/2}) = 3.3$
- Reference 32 should be: Stenstrom M, Olsson J, Mellstrom D. Thyroid hormone replacement is not related to increased risk of osteoporosis. *Osteoporos Int* 2000;11(suppl 2):S144.

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